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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/060,294	04/15/98	JENSEN M	P60953US1

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EXAMINER	
ROMEO,D	
ART UNIT	**PAPER NUMBER**
1647	17

DATE MAILED: 12/18/00

Please find below and/or attached an Office communication concerning this application or pr c eding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/060,294	Jensen et al.
Examiner	**Group Art Unit**
David Romeo	1647

☒ Responsive to communication(s) filed on *4 Oct 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *50-76* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *50-76* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647.

2. The amendment filed 7/20/00 (Paper No. 13) has been entered in part. The amendment to the Abstract has not been entered because a new abstract on a separate sheet is required. The amendments to the specification at page 50, lines 27 and 28, have not been entered because the indicated insertion points do not occur at the indicated positions. The claim amendments have been entered.

3. The amendment filed 10/04/00 (Paper No. 15) has been entered.

4. Claims 50-76 are pending and being examined.

5. Any objection or rejection of record that is not maintained in this Office action is withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The abstract of the disclosure is objected to because it is not a single paragraph. Correction is required. See MPEP § 608.01(b). A new abstract on a separate sheet is required. Applicants attempt to amend the Abstract is noted. However, a new abstract on a separate sheet is required.

7. The application is not fully in compliance the sequence rules, 37 C.F.R. § 1.821-1.825. The specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See pages 37, 43, Figures-3a, -3b. This is not meant to be an exhaustive list of places where the specification fails to recite the appropriate sequence identifiers. The application cannot issue until it is in compliance. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply with the sequence rules. Amino acid sequences with 4 or more residues, at least 4 of which are specifically defined, must comply with the sequence rules. Applicant may bring the Figures into compliance by amending either the Figures or the "Brief Description of the Drawings" to recite the appropriate sequence identifier. Applicants' amendment filed 07/20/00 (Paper No. 13) is noted. However, the sequence listing does not contain a "SEQ ID NO: 339737". Furthermore, the amino acid sequence (Figure 3b) and the nucleotide sequence (Figure 3a) require separate identifiers.

Correction is required.

8. Claims 1-28, 32, 40-45, 47 were rejected under 35 U.S.C. 103(a) as being unpatentable over Mouritsen et al. (AV, cited by Applicants) in view of Pennica et al. (BP, cited by Applicants), Shirai et al. (BN, cited by Applicants), or Wang et al. (BL, cited by Applicants), further in view of Jones et al. (BF, cited by Applicants), and/or further in view of Panina-Bordigon et al. (BO, cited by Applicants).

The rejection of record, incorporated herein by reference, is applied to claims 50-76.

Applicants' arguments have been fully considered but they are not persuasive. Applicants' reference to the responses given in the first and second written opinions is acknowledged. However, the responses given in the first and second written opinions are not of record and the examiner cannot comment on evidence that is not of record.

Applicants argue that the prior art is not enabling because there is a lack of predictability and guidance in the art. The examiner fails to see the distinction between neutralization of TNF and enhanced clearance of TNF via antibodies thereto, in terms of the end result, which is a TNF biological activity diminution. Mouritsen (AV) clearly teaches that injection of recombinant proteins, which have been appropriately modified by the insertion of foreign T cell epitopes, induces an autoantibody response against the recombinant protein. By using this principle for developing vaccines against undesirable proteins, the risk of inducing allergic side-reactions is reduced, and toxic self proteins can simultaneously be detoxified by removing or mutating biologically active segments (page 6, line 29, through page 7, line 15). Furthermore, Mouritsen

(AV) clearly teaches the induction of anti-TNF antibodies in order to affect TNF-mediated diseases (page 14, lines 26-30), which provides a motivation, teaching and guidance to produce TNF neutralizing anti-TNF antibodies. There is a clear motivation, teaching, and suggestion in Mouritsen (AV), taken as a whole, to modify TNF so that neutralizing antibodies to TNF could be raised. The success of Mouritsen (AV) in raising antibodies to mouse TNF provides a reasonable expectation of success that antibodies to other TNFs could be raised. Mouritsen (AV) also provides the motivation to select those antibodies that neutralize TNF. Namely, the modified TNF could be administered as an anti-TNFα vaccine to individuals suffering from diseases where TNFα is important for the pathogenesis. Mouritsen (AV) also provides an assay for the measurement of TNF bioactivity. Specifically, the L929 bioassay for TNFα (page 12, lines 16-17). It would require no more than routine experimentation for one of ordinary skill in the art to make modified murine TNF molecules, raise antibodies to such modified TNFs, and screen those antibodies for neutralization of TNF biological activity, in the L929 bioassay for TNFα. It is obvious from the disclosure of Mouritsen (AV) that it is necessary to make modified TNF molecules that are devoid of significant biological activity and at the same time are capable of raising neutralizing antibodies to unmodified TNF. Jones (BF) clearly indicates regions in TNF of functional importance for receptor binding and biological activity (paragraph bridging pages 113-114 through paragraph bridging pages 122 and 124, and the tables and figures therein). "Thus a drastic reduction in biological activity points to the involvement of such residues in the functional

interaction of the TNF trimer ... with the receptor". See Jones (BF), sentence bridging pages 117 and 119. Jones (BF) also teaches a putative receptor binding site involving residues 11 to 13, 37 to 42, 49 to 57, and 155 to 157 and mutations in amino acid residues that abrogate TNFα activity (Jones, Tables 2 and 3). . It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to substitute the p2 (15 amino acids) and p30 (21 amino acids) such that the insertion occurred in the region 11 to 13, 37 to 42, 49 to 57, and 155 to 157. Substitution of a region comprising 49 to 57 or a portion thereof with p2 or p30 would involve a segment of the D strand of the back β sheet, as recited in claim 54. Substitution of amino acid 143, 146, 147, or 148 (mutations that abrogate biological activity, see Jones, Figure 13) or a portion of a region comprising amino acids 143, 146, 147, or 148 with p2 or p30 would be a substitution that comprises at least a segment of the H strand of the front β sheet and of the connecting loop to the I strand, as recited in claim 55, or wherein the substitution comprises amino acids 132 to 146 as recited in claim 56, or wherein the substitution comprises segments of the H and I strands and the entire connecting loop, as recited in claim 57. The loop connecting the D and E strands comprises amino acids 68 to 75. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to substitute the loop connecting the D and E strands with p2 or p30 with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to abrogate TNFα activity. Such a substitution would comprise a segment of the D strand, at least a segment of the E strand and the

entire connecting loop, as recited in claim 58. Substitution of the loop connecting the D and E strands with p2 or 30 would comprises substitution of amino acids 65 to 79, as recited in claim 59. Substitution of amino acids 37 to 42 or 49 to 57 with p2 or p30 would comprise substitution of the entire C' and C strands and a segment of the D strand, as recited in claim 60, or with p30 would comprise substitution of amino acids 40 to 60, as recited in claim 61. Such a substitution would comprise at least a segment of the E strand (amino acids 76-83) and of one or both of the connecting loops (amino acids 68-75 or 84-90), as recited in claim 62, or comprise amino acids 76 to 90, as recited in claim 63. SEQ ID NOs: 4, 8, and 10 comprises substitutions of amino acids 66-80, 133-147, and 77-91, respectively, with p2. SEQ ID NOs: 14, 16, and 20 comprise substitution of amino acid residues 41-61, 65-85, and 132-152, respectively, with p30. Each of amino acid residues 66-80, 133-147, 77-91, 41-61, 65-85, and 132-152 comprise regions that abrogate or substantially reduce TNFα bioactivity or are areas of putative receptor binding. See Jones, Tables 2 and 3, and Figures 13 and 14.

Jones also teaches an antibody with an epitope involving Arg 131 that neutralizes TNF and that binds sufficiently close to the putative receptor binding site to block the receptor (paragraph bridging pages 118 and 120). It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to mutate those sites by insertion of an immunodominant T cell epitope, and one of ordinary skill in the art would have a reasonable expectation that such a modified TNF molecule would be substantially free from TNFα activity

because the residues that are critical for receptor binding had been substituted, modified and/or deleted and one of ordinary skill in the art would have a reasonable expectation that antibodies generated to the regions flanking the immunodominant T cell epitope would bind sufficiently close to the putative receptor binding site to block receptor binding. Jones also teaches the distribution of mutations in the connecting loops that abrogate biological activity (Figure 13)

9. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 76 is indefinite over the recitation of "iscom" because acronyms are arbitrarily assigned and their meaning is ambiguous. It is suggested that the acronym be spelled out.

New formal matters, objections, and/or rejections:

Specification

10. The amendment filed 07/20/00 (Paper No. 13) is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "SEQ ID NO: 339737 Gen Bank Accession No. M10988". Revisions or updates to GenBank entries can be made at any time. The interpretation

of a reference to a GenBank entry is dependent upon the particular revision, update or release date of that particular entry. This is because if GenBank sequences are amended and accession numbers do not change, the metes and bounds of the invention may change. A sequence previously not included at filing may be included as a result of a revision or update to the GenBank entry. An included sequence previously not included at filing is new matter. Applicant must establish that the sequences present in the GenBank data base are the same sequences in Figure-3a and -3b as of the filing date of the application.

Applicant is required to cancel the new matter in the reply to this Office action.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 6:45 A.M. TO 3:15 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

OFFICIAL PAPERS FILED BY FAX SHOULD BE DIRECTED TO (703) 308-4242.

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DECEMBER 17, 2000